## REMARKS

Claims 1, 3-5, 9-11, and 13-25 remain in the application for further examination.

Reconsideration of this application, and entry of the foregoing amendments is respectfully requested.

The specification has been amended at page 1, as requested by the Examiner, to introduce the reference to the prior application.

It is submitted that the objection to the drawings has been overcome by the amendment to the figure legend of Figure 4. In a related matter, the specification was amended at pages 4, 7 and 8 to introduce the five panels (A-E) instead of the three as in the original application(because of the smaller font used originally).

As requested by the Examiner, the figure legend of Figure 1 was amended so as to refer to each panel. The Examiner will also note that the figure legend of Figure 4 was amended so that the initiator AUG is now "boxed" instead of the previous recitation of "bold", and Figure 4A has been amended accordingly. In addition, erroneous reference to the "transcription start site ATG", as opposed to "the translation start site ATG", has been corrected. Page 8 was also amended to correct the clerical errors relating to the ORF and intron, as supported by Figs. 4A-4E and the figure legend therefor as well as in Appendix A supplied with the response of June 28, 2002 and the arguments presented below.

PTO-1449 forms are submitted herewith in order to have the references cited in the Search Report considered, in accordance with the Examiner's instructions.

## OBJECTION UNDER 35 U.S.C. § 132

The Examiner objects to the amendments filed December 1st, 2001 and November 9, 2001 as introducing new matter in the disclosure. While the Examiner considers that SEQ ID NO:5 is supported by the original disclosure, she is of the opinion that the protein sequence encoded thereby "is not supported by the original disclosure". The Applicant once again apologizes for the confusion which stems from the lack of clarity and clerical errors which describe the open-reading frame present in SEQ ID NO:5. Once again, the Applicant submits that the open-reading frame set

forth in SEQ ID NO:6 is indeed supported by the sequence as originally filed and disclosure as originally filed. For example:

1) The initiator AUG is at position 490 and is preceded by 19 bps of non-coding exon sequences as described in the filed application.
2) The encoded ORF is a very long 1755 aa ORF and contains 14 glutamines (Gln) (1320-1362 in SEQ ID NO:5) as described in the specification as originally filed (Figure 4) as well as at position 191-232 of SEQ ID NO:2, which is based on the sequence present in the priority application.
3) The present invention teaches primers (SEQ ID NO:3 and 4) which enable an amplification of the nucleic acid region encoding the glutamine repeats.
4) The alignment between hGT1 and its mouse homolog in Figure 3 and lines 1-19 in the specification which refer to the mouse GT1 protein and its homology to the hGT1 and
5) Of course the teaching that the hGT1 sequence "includes a 5535 base pair open-reading frame without interruption.

The argument of the Examiner concerning the ATG in bold in Figure 4 has been addressed above by the amendment to the figure legend of Figures 4A-4E. Applicant submits that the replacement of the term "transcription start site" by "translation start site" does not constitute new matter and should clearly be viewed as correcting a clerical error. Indeed, in view of the significantly long open-reading frame which initiates at the now boxed ATG, it should be clear that the inventors intended the terminology "translation start site".

With respect to the numerous stop codons, the Applicant submits the following. While admittedly the 3' end of SEQ ID NO:5 contains stop codons, it should be clear to the Examiner that until the first stop codon is reached in SEQ ID NO:5, a very significantly long open-reading frame is encoded thereby (1755 amino acids).

In any event, the statement "TG1 includes 5535 base pairs bps open-reading frame (ORF) of 5535 base pairs without interruption", has been corrected.

Applicant hereby cancels SEQ ID NO:7-10 and will provide in the near future a substitute sequence listing deleting same together with the amendments to the specification and claims to bring same in line with this new sequence listing.

It is respectfully submitted that in view of the cancellation of SEQ ID NO: 7-10, that the concerns of the Examiner the small peptide sequences at the 3' end of SEQ ID NO:5 have been overcome.

Claims 19-25 have been rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey the one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Applicant respectfully refers the Examiner to the arguments above which are summarized again hereinbelow. The fact that the disclosed and supported SEQ ID NO:5 encodes a protein is submitted to be therefore clearly supported by the specification as originally filed. In addition, the Examiner is referred to the following teachings in the specification.

At page 3, lines 32-35:

> "CAG repeats are often very polymorphic and have been found to be over represented in coding sequences of the human genome particularly those coding for DNA-binding proteins/transcription factors." [emphasis added]

At page 4, between lines 5 and 7:

> "CAG repeats **(or the polyglutamine stretches for which they encode)** might modulate the function of the genes **(or protein)**" [emphasis added]

At page 9, between lines 7 and 9:

> "First, the presence of a splice acceptor upstream of the ORF suggest that the pre-mRNA will be processed." [emphasis added]

At page 9, lines 12-17:

> "Sequencing of the previously described hGT1 alleles showed that they code for 10 to 14 glutamines (Q). The CAG-repeat is generally constituted of 9 to 13 CAG repetitions followed by CAA ($CAG_{9-13}CAA$) with the exception of the 13Q allele which is $CAGCAACAG_{10}CAA$." [emphasis added]

Finally, Table 2, at page 16 shows the number of PNQ "potential number of encoded polyglutamines" (see the table legend of Table 2) and hGT1 (GCT10D04) showing 14 such PNQ.

In view of the above and foregoing, it should be clear and without question that the encoded open-reading frame or protein of SEQ ID NO:5 (SEQ ID NO:6) is supported and taught in the specification as originally filed. Of course, the Applicant realizes that a figure showing the amino acid sequence of the encoded ORF would have been advantageous. Nevertheless, the Applicant respectfully requests that the Examiner withdraws her objection of the new matter rejection of the long, taught and intrinsic open-reading frame encoding the protein defined in SEQ ID NO:6 and ending at amino acid 1755, as it should now be clear that it does not constitute new matter. Applicant reiterates that SEQ ID Nos: 7-10 are cancelled.

With respect to the teachings of vectors and cells, the Applicant respectfully submits that the concept of expressing the sequences of the present invention containing the CAG repeats encoding the polyglutamine stretches of the present invention is taught, for example at page 5, from line 33 and carrying over to line 4 of page 6, as originally filed. It is taught therein that a mammal model is designed by modifying its cells so that they "now express at least one allelic variant of the hGT1 gene and wherein the allelic variant of the hGT1 being introduced into the mammal or an ancestor of the mammal...". It is respectfully submitted that a person of ordinary skill in the art would understand that such germ cells or somatic cells are genetically engineered so as to express a sequence of the present invention. It should also be understood by a person of ordinary skill in the art that vectors would be required to express same. In view of the above and foregoing, the Applicant respectfully requests that the Examiner withdraws her objection of the claims relating to vectors and cells.

**REJECTIONS UNDER 35 U.S.C. § 112, first paragraph (Written Description)**

Claims 1-5, 9-11 and 13-25 have been rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey the one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

The Applicant respectfully traverses the rejection as follows. At the time of filing, the Applicant had identified and characterized the hGT1 gene (6022 nucleotides) and its encoded protein comprising the sequence of 1755 amino acids described in SEQ ID NO:6. While admittedly SEQ ID NO:5 contains a sequencing error in the last 250 nucleotides of the 6022 nucleotide sequence, at the time of filing the Applicant was in possession of a significant portion (approximately 95%) of the hGT1 encoded protein, and had determined that it comprised polymorphic regions which could be linked to psychiatric diseases having the characteristics defined in the claims.

The Examiner then compares the instant application to Examples 6 and 7 in the written description guidelines. The Applicant respectfully disagrees since in view of the 1755 amino acid sequence which is described, and of the fact that the polymorphic region of the hGT1 gene sequence is but a fraction thereof, the Applicant respectfully submits that claims directed to the isolated human hGT1 gene sequences are clearly and adequately described and should therefore be recognized as such by one skilled in the art.

The Applicant respectfully disagrees with the Examiner, with respect to the rejection based on SEQ ID NO:5 being a partial cDNA, , since SEQ ID NO:5 which teaches the sequence shown in Figures 4A-4E, also includes (as taught in the figure legend of Figure 4) intron sequences in lower case in 4A and between positions 1 to 470 of SEQ ID NO:5.

With respect to the objection of the Examiner concerning the coding potential of SEQ ID NO:5, while admittedly it contains 3 stop codons in the last 5% thereof (not the "middle of SEQ ID NO:5" as suggested by the Examiner) in view of the arguments provided above, it should be clear that the coding potential of SEQ ID NO:5 is clearly and distinctly enabled and described in the application as originally filed.

Once again, the Examiner is reminded that since the CAG or CAA repeats encode glutamine, and since there is ample teaching of glutamine repeats in hGT1 in

the original filed application, the Applicant respectfully requests that the Examiner withdraws her rejection.

**REJECTIONS UNDER 35 U.S.C. § 112, first paragraph (Scope of Enablement)**

Claims 1-5, 9-11 and 13-25 have been rejected under 35 U.S.C. § 112, first paragraph because the specification, while being enabling for short CAG repeat allelic variants of hGT1 associated with schizophrenia, it does not provide enablement for any disorder. The Examiner, while considering that the application is "enabling for short CAG repeat allelic variants of hGT1 associated with schizophrenia, it does not provide enablement for any allelic variants of hGT1 associated with any disorder such as psychiatric diseases..." Applicant respectfully submits that in view of the teachings of the present invention, and for example the teachings at page 23, between lines 8-34 and in particular between lines 30-34, that claims 1-5, 9-11 and 13-25 would be considered enabled by a person of ordinary skill in the art to which the present invention pertains.

With respect to the lack of clarity alleged by the Examiner concerning the short and long alleles, the Applicant provides the following, while acknowledging that different nomenclatures and different polymorphisms make the present invention rather complex to comprehend. While the most common allele is indeed that when n=11, in the CAG repeat found in claim 1 $(CAR)_2(CAG)_nCAA$, indeed equals to 14 (CAR encoding two glutamines; $(CAG)_{n=11}$ encoding eleven glutamines and CAA encoding the fourteenth glutamine residue). In addition, the Examiner is correct in comprehending that n=11 is a control and hence, when n is different than 11, the human gene sequence associated therewith is associated with schizophrenia. For clarity, claim 15 relates to the sequence of the most common allele (n control), while claim 13 relates to variants linked to schizophrenia.

Accordingly, in view of the above and foregoing, withdrawal of the rejections under 35 U.S.C. § 112, first paragraph is respectfully solicited.

**REJECTIONS UNDER 35 U.S.C. § 112, second paragraph**

Claims 1-5, 9-11 and 13-25 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Firstly, claims 1-5, 9-11 and 13-25 are considered indefinite because it is alleged that the designation hGT1 is arbitrary. In accordance with the suggestion of the Examiner, claim 1 has been amended by providing a descriptive characterization of the claimed polypeptide.

Secondly, claims 1-5, 9-11 and 13-25 are considered indefinite because the Examiner considers that it is unclear whether Applicant is claiming a nucleic acid sequence which is normal or whether Applicant is claiming variants of the normal which are associated with a disease. Applicant respectfully submits that in view of the arguments presented above clarifying when n=11, and the control allele as opposed to when n is different than 11 and is associated with schizophrenia (as recited in claim 13) that the metes and bounds of the claimed invention is clear.

Thirdly, claims 3-4 are considered indefinite over the recitation "shorter than allele 0, which corresponds to n=11" because according to the Examiner, it is unclear whether the claim encompasses alleles shorter than allele 0 or rather are directed to alleles shorter than allele 0 which are n=11. In view of the deletion of the recitation "than allele 0, which corresponds to" in claims 3, 4, 9 and 10, it is respectfully submitted that this rejection has been rendered moot.

Moreover, claim 3 is considered indefinite because of the term "less severe schizophrenia" which is a relative term. In view of the teachings at page 21 between lines 8 and 14 that there is "a significant correlation between the size of the hTG1 CAG repeat and the pattern of severity of the disease (the longer is the CAG repeat the more severe is the outcome)...regardless of the quality of the response to neuroleptic medication", the Applicant respectfully submits that a person of ordinary skill in the art would consider the term "less severe schizophrenia" as clear and definite. Claims 4-5 and 9 are considered indefinite over the recitation "are indicative of a neuroleptic response" because it is allegedly unclear "based upon the claim and the specification what is encompassed by a neuroleptic response". The Applicant respectfully disagrees with the Examiner's contention. It should be clear throughout

the disclosure, for example, at page 1 between line 32 carrying over to page 3 line 3, as well as at page 3 between lines 17-22, that a neuroleptic response clearly defined as response which improves symptoms of a patient (see for example between line 35 of page 1 to line 3 of page 2).

Claim 9 is considered indefinite because it does "not recite a positive process step which clearly relates back to the preamble". In view of the amendment to claim 9, the Applicant respectfully submits that claim 9 is clear is definite.

Accordingly, in view of the above and foregoing, withdrawal of the rejections under 35 U.S.C. § 112, second paragraph is respectfully solicited.

**REJECTION UNDER 35 U.S.C. § 102(b)**

Claims 1-2, and 13-14 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Neri et al.

The Examiner considers that in view of Neri's teachings of a nucleic acid comprising $CAG_{20}CAA$, that "the structural limitations of the claims have been met and the product is anticipated." The Examiner also claims that "SEQ ID NO:19 of Neri teaches a nucleic acid from chromosome 3p 14 which comprises (has) $CAG_{20}CAA$ (see page 22, line 2 of the Sequence Listing). Therefore, Neri teaches an isolated nucleic acid having the sequence of SEQ ID NO:12-17".

Applicant respectfully traverses the Examiner's rejection as follows. Claims 1-2 and 13-14 in essence teach nucleic acid sequence having the sequence $(CAR)_2(CAG)_nCAA$". Assuming that CAR is CAG, this sequence could be simplified into $(CAG)_{n+2}CAA$. Since n is defined as being from 7 to 12, the sequences of the present invention therefore are from $CAG_9CAA$ (when n=7) to $CAG_{14}CAA$ (when n=12). Clearly, these sequences are not taught nor suggested by the $CAG_{20}CAA$ sequence of Neri. Consequently, the Applicant respectfully requests that the Examiner withdraws her rejection of claims 1-2 and 13-14 under 35 U.S.C. ∋ 102(b).

**CONCLUSIONS**

The rejections of claims 1-5, 9-11 and 13-25 are believed to have been overcome by the present remarks, and by the amendments to the claims. From the

foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such an action is earnestly solicited.

In the event that there are any questions concerning the Amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that the prosecution of the application may be expedited.

Authorization is hereby given to charge Deposit Account no. 19-0036 for any deficiencies or overages in connection with this Response.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned "**Version with markings to show changes made"**.

In the event that there are any questions concerning the amendment or application in general, the Examiner is respectfully urged to telephone the undersigned so that the prosecution of the application may be expedited.

Authorization is hereby given to charge deposit account no. 05-1323 for any deficiency in fees or for credit of any overpayment in connection with this response.

Respectfully submitted,

March 13, 2003

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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

Underlines indicate insertions and brackets "[ ]" indicate deletions.

**IN THE SPECIFICATION:**

At page 1, please insert the following: "This application is a National Stage application of PCT/CA98/00884, filed September 18, 1998."

At page 4, please amend lines 10-13 so that they now read:

"In accordance with the present invention there is provided a hGT1 gene containing transcribed polymorphic CAG repeat, which comprises a sequence as set forth in Fig. 3 and Figs. 4A-4[C]E."

At page 7, please amend lines 14-19 so that they now read:

"Fig. 1 illustrates the average allelic lengths of the GCT10D04 EST CAG repeat in controls, responsive (R) and non-responsive (NR) patients, showing the shorter (s) allele only (Fig. 1A), longer (L) allele only (Fig. 1B) and the sum (L+S) of the two alleles (Fig. 1C) in the three groups of subjects;".

At page 7, please amend lines 27-30 so that they now read:

"Figs. 4A-4[C]E illustrate the nucleotide sequence of hGT1, wherein the upstream intron is in lowercase; Human gene sequence (exon) is in upper case; and the [transcription] translation start site ATG [in bold] is boxed (SEQ ID NO:5). ".

At page 8, please amend lines 30-32 so that they now read:

"The GT1 sequence which includes an [5535 bp] open-reading frame (ORF encoding 1755 amino acids without interruption) [showing] shows 85% homology to the mouse cDNA (Figs. 4A-4[C]E). The sequence of GT1 is from one large (5276 bp) Bam HI fragment and three Pst I fragments (672, 200 and 371 bps). This ORF is preceded by [a] 490 bps, including a 470 bps intron"

**IN THE CLAIMS:**

1. An isolated human hGT1 gene sequence comprising a transcribed polymorphic CAG repeat having the sequence $(CAR)_2(CAG)_nCAA$, wherein R is A or

G and n is from 7 to 12 as set forth in SEQ ID NOs:12-17, wherein allelic variants of said CAG repeat are associated with a disorder selected from the group consisting of psychiatric diseases, schizophrenia, affective disorders, neurodevelopmental brain diseases and phenotypic variability with respect to long term response to neuroleptic medication, and wherein n being equal to 11 (SEQ ID NO:6) is the most common allele of the hGT1 gene;
and wherein said polymorphic CAG repeat encodes a polyglutamine repeat having the sequence GlnGln$(Gln)_n$Gln, wherein n is from 7 to 12.

2. (Amended) The gene sequence of claim 1, wherein said affective disorder is manic depression.

3. (Thrice amended) A method for evaluating the severity of schizophrenia of a patient, which comprises the steps of:

a) obtaining a nucleic acid sample of said patient; and
b) determining allelic variants of said CAG repeat of the gene sequence of claim 1,

wherein allelic variants shorter than [allele 0, which corresponds to] when n=11 (SEQ ID NO:16), are indicative of less severe schizophrenia in the patient.

4. (Twice Amended) A method for the identification of the response of a patient to neuroleptic medication, which comprises the steps of:

a) obtaining a nucleic acid sample of said patient; and
b) determining allelic variants of said CAG repeat of the gene sequence of claim 1,

wherein allelic variants shorter than [allele 0, which corresponds] when n=11, are indicative of a neuroleptic response by said patient.

9. (Twice Amended) A method of categorizing a psychiatric patient according to its genotype in order to maximize its response to treatment to at least one neuroleptic drug, which comprises the steps of:

a) obtaining a nucleic acid sample of said patient; and
b) determining allelic variants of said CAG repeat of the gene sequence of claim 1,

wherein a patient is categorized with respect to his allelic variants, and wherein allelic variants shorter than [allele 0, which corresponds to] when n=11, are indicative

of a neuroleptic response of said patient, thereby categorizing said psychiatric patient according to its genotype to maximize neurolopeptic drug treatment.

10. (Twice Amended) A method of identifying a patient which is responsive to a neuroleptic medication which comprises:

a) obtaining a sample from said patient; and

b) determining allelic variants of said CAG repeat of the gene sequence of claim 1,

wherein allelic variants shorter than [allele 0, which corresponds to] when n=11, identify said patient as a neuroleptic responder.

13. (Twice Amended) The human gene sequence of claim 1, wherein n is selected from the group consisting of 7, 8, 9, 10 and 12, and wherein said allelic variant is associated with schizophrenia.

14. (Twice Amended) The human gene sequence of claim 13, wherein n is selected from:

a) n is 7 to 10, wherein said allelic variant is associated with a neuroleptic medication-responsive status of a schizophrenic patient, and

b) n is equal to 12, wherein said allelic variant is associated with a poor responsive status of a schizophrenic patient to neuroleptic medication.

15. (Amended) The human gene sequence of claim 1, wherein n is equal to 11, which comprises the sequence as set forth in SEQ ID NO:2.

16. (Amended) The human gene sequence of claim 15 comprising the sequence as set forth in SEQ ID NO:5.

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CCCCACCTCCTCCACCTACTCCTCCTCTGTCCAGGGTGGTGGGCA
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AGCGGGTCCAGAATCTTCATGCCTACCAGTCGGGCCGCCTCAGCT
ATGACCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG
CAAGCCCTTCAGAGCCGGCACCATGCCCAGGAAACCCTCCATTAC

Fig. 4A